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(54) Title: METHOD FOR THE TREATMENT OR PREVENTION OF *FLAVIVIRUS* INFECTIONS USING NUCLEOSIDE ANALOGUES

(57) Abstract: The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula (I) or a pharmaceutically acceptable salt thereof.

METHOD FOR THE TREATMENT OR PREVENTION OF *FLAVIVIRUS* INFECTIONS USING NUCLEOSIDE ANALOGUES

FIELD OF THE INVENTION

The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues.

BACKGROUND OF THE INVENTION

Hepatitis is a disease occurring throughout the world. It is generally of viral nature, although there are other causes known. Viral hepatitis is by far the most common form of hepatitis. Nearly 750,000 Americans are affected by hepatitis each year, and out of those, more than 150,000 are infected with the hepatitis C virus (HCV).

HCV is a positive-stranded RNA virus belonging to the *Flaviviridae* family and has closest relationship to the pestiviruses that include hog cholera virus and bovine viral diarrhea virus (BVDV). HCV is believed to replicate through the production of a complementary negative-strand RNA template. Due to the lack of an efficient culture replication system for the virus, HCV particles were isolated from pooled human plasma and shown, by electron microscopy, to have a diameter of about 50-60 nm. The HCV genome is a single-stranded, positive-sense RNA of about 9,600 bp coding for a polyprotein of 3009-3030 amino-acids, which is cleaved co- and post-translationally by cellular and two viral proteinases into mature viral proteins (core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). It is believed that the structural proteins, E1 and E2, the major glycoproteins are embedded into a viral lipid envelop and form stable heterodimers. It is also believed that the structural core protein interacts with

the viral RNA genome to form the nucleocapsid. The nonstructural proteins designated NS2 to NS5 include proteins with enzymatic functions involved in virus replication and protein processing including a polymerase, protease and helicase.

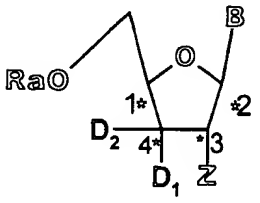
The main source of contamination with HCV is blood. The magnitude of the HCV infection as a health problem is illustrated by the prevalence among high-risk groups. For example, 60% to 90% of hemophiliacs and more than 80% of intravenous drug abusers in western countries are chronically infected with HCV. For intravenous drug abusers, the prevalence varies from about 28% to 70% depending on the population studied. The proportion of new HCV infections associated with post-transfusion has been markedly reduced lately due to advances in diagnostic tools used to screen blood donors.

The only treatment currently available for HCV infection is interferon-α (IFN-α). However, according to different clinical studies, only 70% of treated patients normalize alanine aminotransferase (ALT) levels in the serum and after discontinuation of IFN, 35% to 45% of these responders relapse. In general, only 20% to 25% of patients have long-term responses to IFN. Clinical studies have shown that combination treatment with IFN and ribavirin (RIBA) results in a superior clinical response than IFN alone. Different genotypes of HCV respond differently to IFN therapy, genotype 1b is more resistant to IFN therapy than type 2 and 3.

There is therefore a great need for the further development of anti-viral agents.

Summary of the invention

The present invention relates to a method for the treatment or prevention of *Flavivirus* infections in a host comprising administering a therapeutically effective amount of a compound having the formula I or a pharmaceutically acceptable salt thereof:

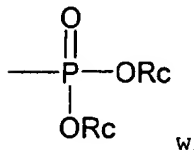


(I)

wherein

B is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, and



wherein each **Rc** are independently chosen from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and an hydroxy protecting group; and

Z is halogen or **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} acyl, or an hydroxy protecting group

D_1 and D_2 are independently selected from N_3, F, or H , D_1 and D_2 can also be joined to be chosen from C_3-cycloalkyl, -=CH_2, or -=CF_2, and

wherein said compound is in the form of a single enantiomer or a mixture thereof including racemic mixtures;

with the proviso that when **B** is adenine, **Z** is **ORb**, D_1 is H, D_2 is H and **Rb** is H, **Ra** is not triphosphate or H.

In another aspect, there is provided a pharmaceutical formulation comprising the compounds of the invention in combination with a pharmaceutically acceptable carrier or excipient.

Still another aspect, there is provided a method for treating or preventing a viral infection in a host comprising administering a combination comprising at least one compound according to formula I and at least one further therapeutic agent.

In another aspect of the invention is the use of a compound according to formula I, for the preparation of a medicament for treating or preventing a viral infections in a host.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the viral infection is chosen from *Flavivirus* infections.

In one embodiment, the *Flavivirus* infection is chosen from Hepatitis C virus (HCV), bovine viral diarrhea virus(BVDV), hog cholera virus and yellow fever virus.

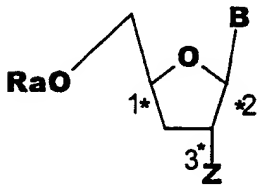
In an other embodiment, the *Flavivirus* infection is Hepatitis C virus.

In one embodiment, there is also provided a method for inhibiting or reducing the activity of viral polymerase

in a host comprising administering a therapeutically effective amount of a compound having the formula I.

In another embodiment, the viral polymerase is HCV polymerase.

The present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ia or a pharmaceutically acceptable salt thereof:

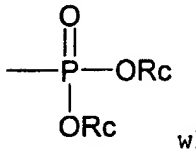


(Ia)

wherein

B is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, and



wherein each **Rc** are independently chosen from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and an hydroxy protecting group; and

Z is halogen or **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} acyl, or an hydroxy protecting group; and

wherein said compound is in the form of a single enantiomer or a mixture thereof including racemic mixtures;
with the proviso that when **B** is adenine, **Z** is **ORb** and **Rb** is H, **Ra** is not triphosphate or H.

In one embodiment, the compounds and methods of the present invention comprise those wherein the following embodiments are present, either independently or in combination.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 1-deaza-adenin-9-yl, 1-deaza-guanin-9-yl, 1-deaza-inosin-9-yl, 1-deaza-2-amino-purin-9-yl, 1-deaza-2-amino-6-chloro-purin-9-yl, 1-deaza-2-6-diamino-purin-9-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl , 2-aza-adenin-9-yl, 2-aza-guanin-9-yl, 2-aza-inosin-9-yl, 2-aza-2-amino-purin-9-yl, 2-aza-2-amino-6-chloro-purin-9-yl, 2-aza-2-6-diamino-purin-9-yl, 3-deaza-thymin-1-yl, 3-deaza-cytosin-1-yl, 3-deaza-uracil-1-yl,5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl

each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl , 2-aza-adenin-9-yl, 2-aza-guanin-9-yl, 2-aza-inosin-9-yl, 2-aza-2-amino-purin-9-yl, 2-aza-2-amino-6-chloro-purin-9-yl, 2-aza-2-6-diamino-purin-9-yl, 3-deaza-thymin-1-yl, 3-deaza-cytosin-1-yl, 3-deaza-uracil-1-yl,5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl
each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-

purin-9-yl 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In a further embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In a further embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, uracil-1-yl, each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-}$

$_{6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In a further embodiment, **B** is cytosin-1-yl, which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In a further embodiment, **B** is guanin-9-yl, which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In a further embodiment, **B** is uracil-1-yl, which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).

In one embodiment, **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, or 1,2,4-triazole-3-carboxamide base (ribarivin base).

In one embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, 5'-fluoro-cytosin-1-yl, 5'-fluorouracil -1-yl or uracil-1-yl.

In one embodiment, **B** is chosen from guanin-9-yl, cytosin-1-yl, 5'-fluoro-cytosin-1-yl, 5'-fluorouracil -1-yl or uracil-1-yl.

In one embodiment, **B** is cytosin-1-yl.

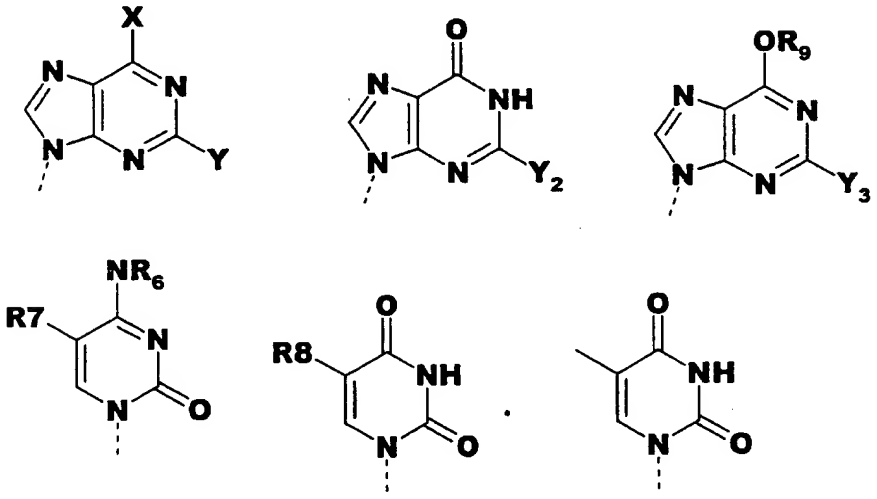
In one embodiment, **B** is 5-fluoro-cytosin-1-yl.

In one embodiment, **B** is 5-fluorouracil.

In one embodiment, **B** is guanin-9-yl.

In one embodiment, **B** is uracil-1-yl.

In a further embodiment, **B** is



Wherein;

X is H, halogen or NHR_{10} , wherein R_{10} is H, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

Y is H, halogen or NHR_{11} , wherein R_{11} is H, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

Y_2 is H, halogen or NHR_{12} , wherein R_{12} is H, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R_9 is H, hydroxy protecting group, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

Y_3 is H, halogen or NHR_{13} , wherein R_{13} is H, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R_7 is H, halogen, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

R_8 is H, halogen, C_{1-6}acyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

In one embodiment,

X is H, halogen or NHR_{10} , wherein R_{10} is H.

Y is H, halogen or NHR_{11} , wherein R_{11} is H.

Y_2 is H, halogen or NHR_{12} , wherein R_{12} is H.

R_9 is H, hydroxy protecting group, C_{1-6} alkyl.

Y_3 is H, halogen or NHR_{13} , wherein R_{13} is H.

R_7 is H, halogen, or C_{1-6} alkyl.

R_8 is H, halogen or C_{1-6} alkyl.

In a further embodiment,

X is H, F, or NHR_{10} , wherein R_{10} is H.

Y is H, F, or NHR_{11} , wherein R_{11} is H.

Y_2 is H, F, or NHR_{12} , wherein R_{12} is H.

R_9 is H.

Y_3 is H, F, or NHR_{13} , wherein R_{13} is H.

R_7 is H, F, or C_{1-6} alkyl.

R_8 is H, F, or C_{1-6} alkyl.

In one embodiment of the invention, **Ra** is chosen from H, monophosphate, diphosphate, and triphosphate.

In another embodiment of the invention, **Ra** is H.

In one embodiment, **Z** is F or **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} acyl, or an hydroxy protecting group.

In one embodiment, **Z** is F.

In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} acyl, or an hydroxy protecting group.

In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, or an hydroxy protecting group.

In one embodiment, **Z** is **ORb**, wherein **Rb** is chosen from of H, or methyl.

In one embodiment, **Z** is **ORb**, wherein **Rb** is H.

D_1 and D_2 are independently selected from N_3, F, or H , D_1 and D_2 can also be joined to be chosen from cyclopropyl, difluorocyclopropyl $-=CH_2$, or $-=CF_2$.

D_1 and D_2 are independently selected from F, or H , D_1 and D_2 can also be joined to be chosen from cyclopropyl, difluorocyclopropyl $-=CH_2$, or $-=CF_2$.

D_1 and D_2 are joined and are cyclopropyl.

D_1 and D_2 are joined and are difluorocyclopropyl.

D_1 and D_2 are joined and are $-=CH_2$.

D_1 and D_2 are joined and are$-=CF_2$.

In one embodiment, D_1 is H or F.

In one embodiment, D_2 is H or F.

In one embodiment, D_1 is H.

In one embodiment, D_2 is H.

In one embodiment, D_1 is F.

In one embodiment, D_2 is F.

In one embodiment, D_1 is N_3 and D_2 is H.

In one embodiment, D_1 is H and D_2 is N_3.

In one embodiment, D_1 is N_3 and D_2 is F.

In one embodiment, D_1 is F and D_2 is N_3.

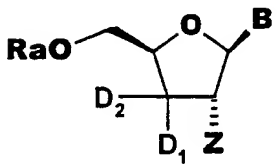
In one embodiment, D_1 is H and D_2 is F.

In one embodiment, D_1 is F and D_2 is H.

In one embodiment, D_1 and D_2 are H.

In one embodiment, D_1 and D_2 are F.

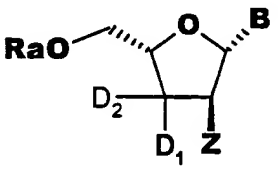
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ib or a pharmaceutically acceptable salt thereof:



(Ib)

wherein **Ra**, **B**, D_1, D_2 and **Z** are as defined above.

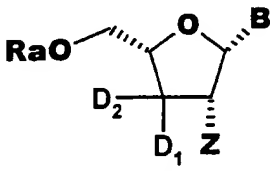
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ic or a pharmaceutically acceptable salt thereof:



(Ic)

wherein **Ra**, **B**, D_1, D_2 and **Z** are as defined above.

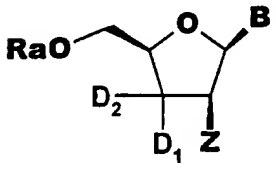
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Id or a pharmaceutically acceptable salt thereof:



(Id)

wherein **Ra**, **B**, D_1, D_2 and **Z** are as defined above.

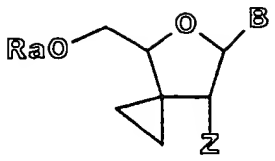
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ie or a pharmaceutically acceptable salt thereof:



(Ie)

wherein **Ra**, **B**, D_1, D_2 and **Z** are as defined above.

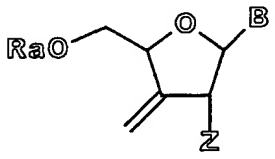
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula If or a pharmaceutically acceptable salt thereof:



(If)

wherein **Ra**, **B**, and **Z** are as defined above.

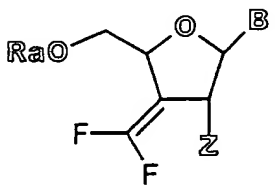
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ig or a pharmaceutically acceptable salt thereof:



(Ig)

wherein **Ra**, **B**, and **Z** are as defined above.

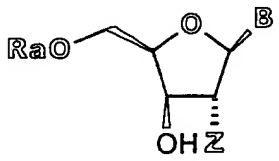
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ih or a pharmaceutically acceptable salt thereof:



(Ih)

wherein **Ra**, **B**, and **Z** are as defined above.

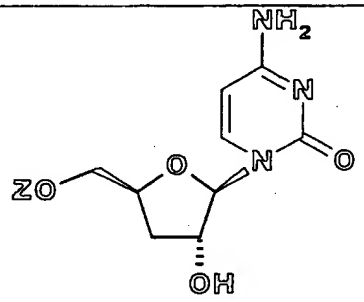
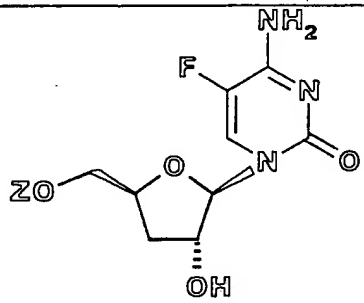
In a further embodiment, the present invention relates to a method for the treatment or prevention of *Flavivirus* infections using nucleoside analogues in a host comprising administering a therapeutically effective amount of a compound having the formula Ii or a pharmaceutically acceptable salt thereof:

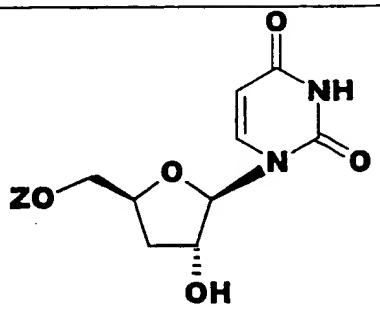
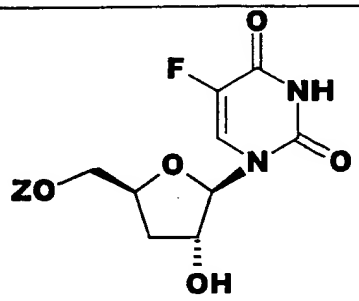
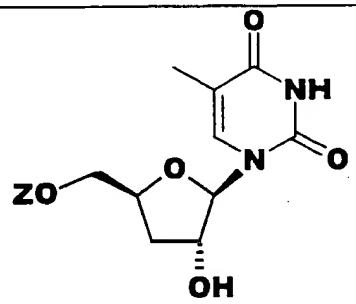
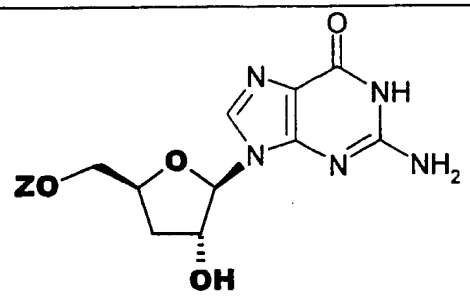


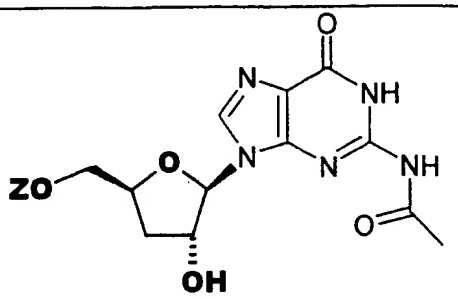
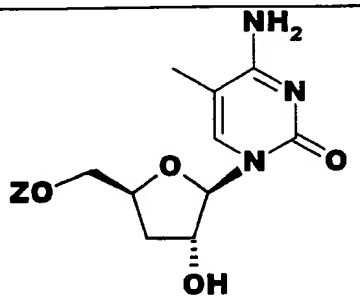
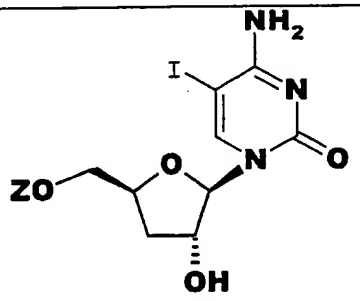
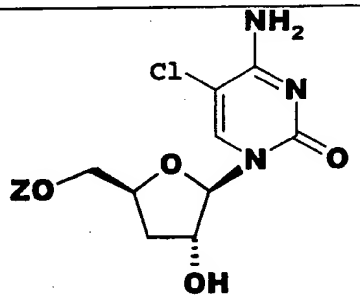
(Ii)

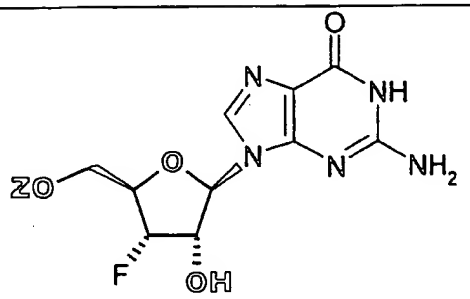
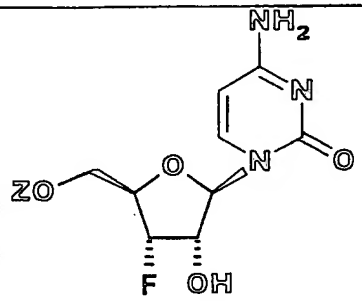
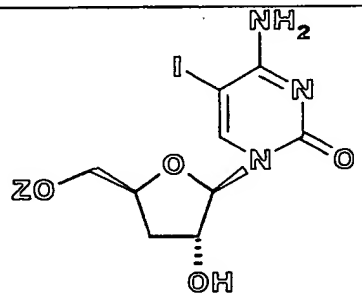
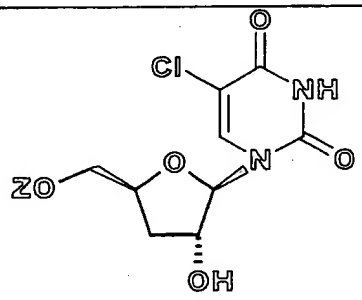
wherein **Ra**, **B**, and **Z** are as defined above.

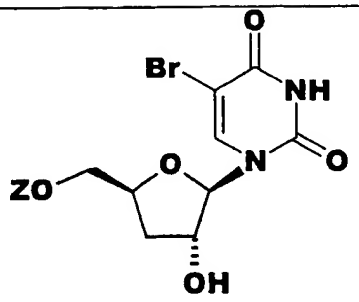
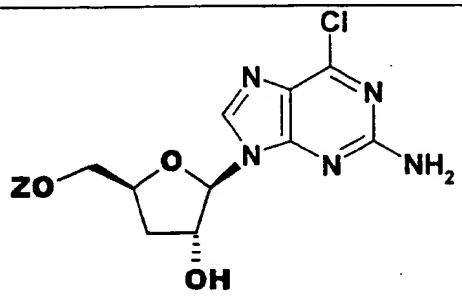
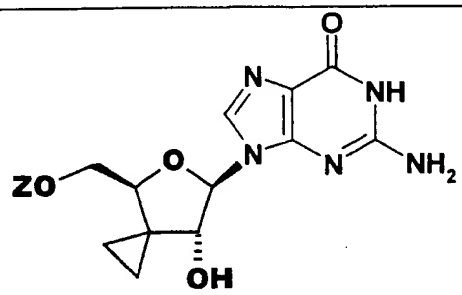
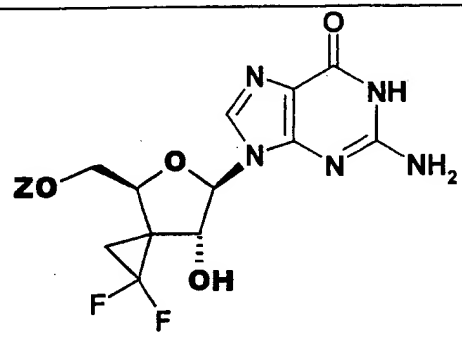
In one embodiment, a compound of formula (I) is chosen from:

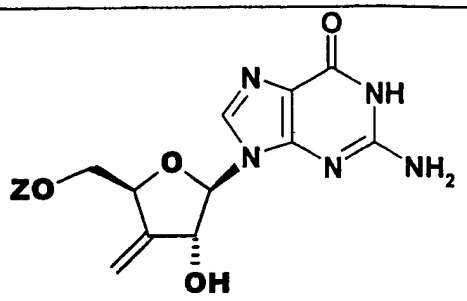
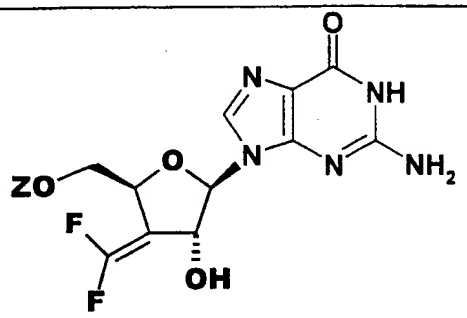
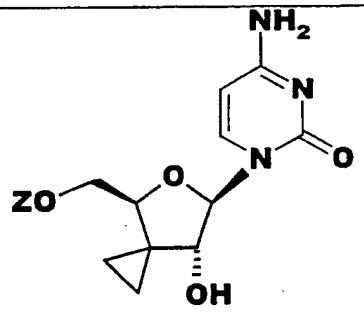
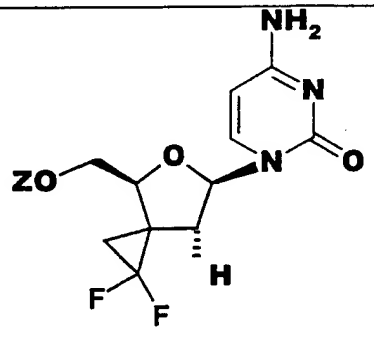
3'-deoxycytidine Z=H, **Compound #1**, 3'-deoxycytidine- 5'triphosphate Z=triphosphate, **Compound #2**	
5-Fluoro-3'-deoxycytidine Z=H, **Compound #3** 5-Fluoro-3'-deoxycytidine- 5'triphosphate Z=triphosphate, **Compound #4**	

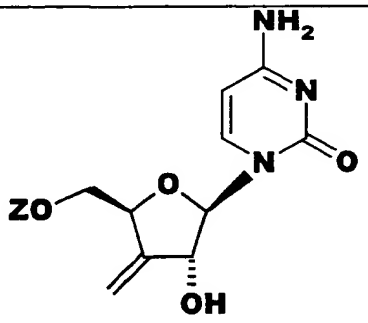
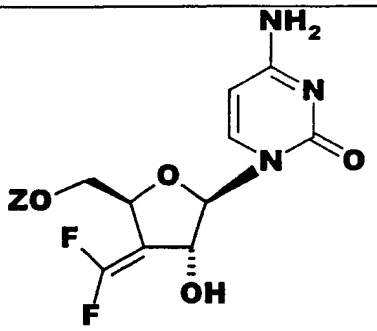
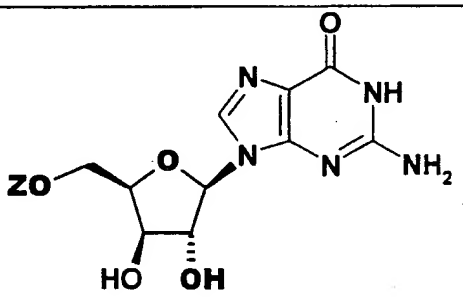
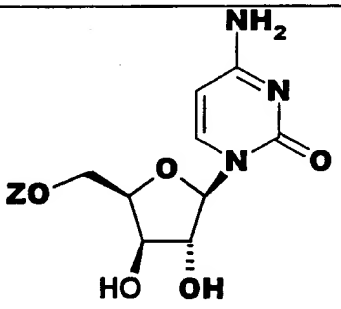
3'-deoxyuridine Z=H, **Compound #5** 3'-deoxyuridine- 5'triphosphate Z=triphosphate, **Compound #6**	
5-Fluoro-3'-deoxyuridine Z=H, **Compound #7** 5-Fluoro-3'-deoxyuridine- 5'triphosphate Z=triphosphate, **Compound #8**	
3'-deoxythymidine Z=H, **Compound #9** 3'-deoxythymidine- 5'triphosphate Z=triphosphate, **Compound #10**	
3'-deoxyguanosine Z=H, **Compound #11** 3'-deoxyguanosine- 5'triphosphate Z=triphosphate, **Compound #12**	

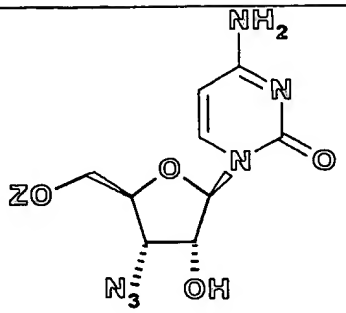
2-N-acetyl-3'-deoxyguanosine Z=H, **Compound #13** 2-N-acetyl-3'-deoxyguanosine-5'triphosphate Z=triphosphate, **Compound #14**	
5-Methyl-3'-deoxycytidine Z=H, **Compound #15,** 5-Methyl-3'-deoxycytidine-5'triphosphate Z=triphosphate, **Compound #16**	
5-Iodo-3'-deoxycytidine Z=H, **Compound #17,** 5-Iodo-3'-deoxycytidine-5'triphosphate Z=triphosphate, **Compound #18**	
5-Chloro-3'-deoxycytidine Z=H, **Compound #19,** 5-=Chloro-3'-deoxycytidine-5'triphosphate Z=triphosphate, **Compound #20**	

3'-fluoro-3'-deoxyguanosine Z=H, **Compound #21** 3'-fluoro-3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #22**	
3'-fluoro 3'-deoxycytidine Z=H, **Compound #23,** 3'-fluoro 3'-deoxycytidine-5'triphosphate Z=triphosphate, **Compound #24**	
5-Iodo-3'-deoxycytidine Z=H, **Compound #25,** 5-=Iodp-3'-deoxycytidine-5'triphosphate Z=triphosphate, **Compound #26**	
5-Chloro -3'-deoxyuridine Z=H, **Compound #27** 5-Chloro -3'-deoxyuridine-5'triphosphate Z=triphosphate, **Compound #28**	

5-Bromo -3'-deoxyuridine Z=H, **Compound #29** 5-Bromo -3'-deoxyuridine-5'triphosphate Z=triphosphate, **Compound #30**	
6-Chloro-3'-deoxyguanosine Z=H, **Compound #31** 6-Chloro -3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #32**	
3'-spirocyclopropyl-3'-deoxyguanosine Z=H, **Compound #33** 3'-spirocyclopropyl-3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #34**	
3'-difluoro-spirocyclopropyl-3'-deoxyguanosine Z=H, **Compound #35** 3'-difluoro-spirocyclopropyl-3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #36**	

3'-methylene-3'-deoxyguanosine Z=H, **Compound #37** 3'-methylene-3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #38**	
3'-difluromethylene 3'-deoxyguanosine Z=H, **Compound #39** 3'-difluromethylene 3'-deoxyguanosine -5'triphosphate Z=triphosphate, **Compound #40**	
3'-spirocyclopropyl-3'-deoxycytidine Z=H, **Compound #41** 3'-spirocyclopropyl-3'-deoxycytidine -5'triphosphate Z=triphosphate, **Compound #42**	
3'-difluoro-spirocyclopropyl-3'- deoxycytidine Z=H, **Compound #43** 3'- difluoro-spirocyclopropyl-3'-	

deoxycytidine -5'triphosphate Z=triphosphate, **Compound #44**	
3'-methylene-3'-deoxycytidine Z=H, **Compound #45** 3'-methylene-3'-deoxycytidine -5'triphosphate Z=triphosphate, **Compound #46**	
3'-difluromethylene 3'-deoxycytidine Z=H, **Compound #47** 3'-difluromethylene 3'-deoxycytidine -5'triphosphate Z=triphosphate, **Compound #48**	
9-β-D-xylofuranosyl-guanosine Z=H, **Compound #49** 9-β-D-xylofuranosyl-guanosine -5'triphosphate Z=triphosphate, **Compound #50**	
9-β-D-xylofuranosyl-cytidine Z=H, **Compound #51** 9-β-D-xylofuranosyl-cytidine -5'triphosphate Z=triphosphate, **Compound #52**	

3'-azido-3'- deoxycytidine Z=H, **Compound #53** 3'-azido-3'- deoxycytidine 5'triphosphate Z=triphosphate, **Compound #54**	

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least three chiral centres and which are marked by **1**, **2** and **3**. When D1 and D2 are different, the compounds of formula (I) contain at least four chiral centres which are marked by **1**, **2**, **3** and **4**. The compounds of formula (I) thus exist in the form of different optical isomers (e.g β-L and β-D) and geometric isomers trans or α and cis or β. All such enantiomers, geometric isomers and mixtures thereof including racemic mixtures are included within the scope of the invention. The single optical isomer or enantiomer can be obtained by method well known in the art, such as chiral HPLC, enzymatic resolution and the use of chiral auxiliary.

According to one embodiment, the atoms marked by 1 and 2 are in the cis or β configuration.

According to one embodiment, the atoms marked by 1 and 2 are in the cis or β configuration while the atom marked by 3 is in a trans or α configuration with respect to the atom 1 and 2.

According to one embodiment, compounds of formula I of the present invention are provided substantially in the form of the β-D configuration.

According to one embodiment, compounds of formula I of the present invention are provided substantially in the form of the β-L configuration.

By "substantially" is meant that there is more one enantiomer then of the other enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 95% free of the corresponding β-D enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 97% free of the corresponding β-D enantiomer.

Still in another embodiment, the compounds of formula I of the present invention are at least 99% free of the corresponding β-D enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 95% free of the corresponding β-L enantiomer.

In another embodiment, the compounds of formula I of the present invention are at least 97% free of the corresponding β-L enantiomer.

Still in another embodiment, the compounds of formula I of the present invention are at least 99% free of the corresponding β-L enantiomer.

There is also provided pharmaceutically acceptable salts of the compounds of formula I of the present invention. By the term pharmaceutically acceptable salts of the compounds of formula (I) are meant those derived from

pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4+ (where R is C_{1-4} alkyl) salts.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used in the present application, "compound(s) of formula (I)" refers to all compounds identified by formula (I) and formulae (Ia) to (Ii).

As used in this application, the term "purine or pyrimidine or an analogue thereof" is meant a purine or pyrimidine base found in nucleotide or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the normal bases but may possess additional or lack certain of the functional properties of the normal bases. Such analogues include those derived by replacement of a

CH moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice versa (for example 7-deazapurines, such as 7-deazadenosine or 7-deazaguanosine) or both (e.g. 7-deaza, 8-azapurines). Analogues of such bases also include those compounds wherein ring substituents are either incorporated, removed or modified by conventional substituents known in the art e.g. halogen, hydroxyl, amino, C1-6 alkyl. Such purine or pyrimidine base, analogues and derivatives will be well known to those skilled in the art.

As used in this application, the term "alkyl" represents an unsubstituted or substituted (by a halogen, nitro, $CONH_2$, COOH, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, O-C_{2-6} alkynyl, hydroxyl, amino, or COOQ, wherein Q is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl) straight chain, branched chain or cyclic hydrocarbon moiety (e.g. isopropyl, ethyl, fluorohexyl or cyclopropyl). The term alkyl is also meant to include alkyls in which one or more hydrogen atoms is replaced by an halogen, more preferably , the halogen is fluoro (e.g. CF_3- or CF_3CH_2-).

As used in this application, the term "cycloalkyl" represents an "alkyl" as defined above which forms a ring.

The terms "alkenyl" and "alkynyl" represent an alkyl containing at least one unsaturated group (e.g. allyl).

The term "hydroxy protecting group" is well known in the field of organic chemistry. Such protecting groups may be found in T. Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 1981). Example of hydroxy protecting groups include but are not limited to acetyl-2-thioethyl ester, pivaloyloxymethyl ester and isopropyloxycarbonyloxymethyl ester.

The term "aryl" represents an unsaturated carbocyclic moiety, optionally mono- or di-substituted with OH, SH, amino, halogen or C_{1-6} alkyl.

The term "heteroaryl" represents an aryl wherein at least one carbon ring atom is substituted by an heteroatom (e.g. N, O, or S).

The term "aminoalkyl" represents an alkyl which is covalently bonded to the adjacent atom through a nitrogen atom.

The term "thioalkyl" represents an alkyl which is covalently bonded to the adjacent atom through a sulfur atom.

The term "alkoxy" represents an alkyl which is covalently bonded to the adjacent atom through an oxygen atom.

Halogen are chosen from F, Cl, I, and Br.

The term "host" represents any mammals including humans.

In one embodiment, the host is human.

The compounds of the present invention are can be prepared by methods well known in the art. For example, such methods are described in the following references *J.Med.Chem.* **1991**, 34, 693-701; *Chem. Pharm. Bull.* **1995**, 43(11) 2005-2009; *J.Org.Chem.* **1989**, 54, 631-635; *Can.J.Chem.* **1975**, 53(19), 2975-2977; *Nucleosides Nucleotides*, **1990**, 9(8), 1045-60 and *Chemistry of Nucleosides and Nucleotides* edited by Leroy B.Towsend, 1988 Plenum Press Volumes 1 and 2; Synthesis of 2'-β-fluoro- and 3'-β-fluoro-substituted guanine nucleosides.

Effect of sugar conformational shifts on nucleophilic displacement of the 2'-hydroxy and 3'-hydroxy group with DAST. J. Org. Chem. , 57(26), (1992) 7315-21. Synthesis and antiviral and cytostatic properties of 3'-deoxy-3'-fluoro- and 2'-azido-3'-fluoro-2',3'-dideoxy-D-ribofuranosides of natural heterocyclic bases. J. Med. Chem. , 34(7), (1991) 2195-202. Synthesis of 9-(3-deoxy-3-fluoro-β-D-ribofuranosyl)guanine, a new potent antiviral agent. J. Chem. Soc., Chem. Commun. (1989) (1989), (14), 955-7. Synthesis and antiviral activity evaluation of 3'-fluoro-3'-deoxyribonucleosides: broad-spectrum antiviral activity of 3'-fluoro-3'-deoxyadenosine. Antiviral Res. (1989), 12(3), 133-50. 3'-Fluoro-3'-deoxyribonucleoside 5'-triphosphates: synthesis and use as terminators of RNA biosynthesis. FEBS Lett. (1989), 250(2), 139-41. Reaction of 1-(2',3'-epoxy-β-D-lyxofuranosyl)uracil with hydrogen fluoride. The unexpected formation of 1-(3'-fluoro-3'-deoxy-β-D-ribofuranosyl)uracil. J. Heterocycl. Chem. (1984), 21(3), 773-5. Synthesis of 3'-deoxy-3'-fluorouridine. J. Carbohydr., Nucleosides, Nucleotides (1975), 2(3), 191-5. Synthesis of the 2'-deoxy-2'-fluoro and 3'-deoxy-3'-fluoro analogs of 8-bromoadenosine. Nucleic Acids Symp. Ser. (1997), 37(Symposium on Nucleic Acids Chemistry, 1997), 17-18. Synthesis of 8-substituted analogs of 3'-deoxy-3'-fluoroadenosine. Nucleosides Nucleotides (1998), 17(1-3), 115-122. A new synthesis of 3'-fluoro-3'-deoxyadenosine. Nucleosides Nucleotides (1991), 10(1-3), 719-21. Synthesis of 3'-fluoro-3'-deoxyadenosine starting from adenosine. Synthesis (1990), (10), 900-5. Synthesis of 3'-deoxy-3'-fluoroadenosine by chemical transglycosidation. Z. Chem. (1989), 29(6), 209-10. Stereoselective synthesis of 3'-deoxy-3'-fluoroadenosine. Bull. Chem. Soc. Jpn. (1989), 62(6), 2119-20. Synthesis of nucleosides fluorinated in the sugar moiety. The

application of diethylaminosulfur trifluoride to the synthesis of fluorinated nucleosides. Nucleosides Nucleotides (1989), 8(1), 65-96. Preparation of difluorouridines as antitumor agents. Efficient removal of sugar O-tosyl groups and heterocycle halogens from purine nucleosides with sodium naphthalenide. Tetrahedron (1997), 53(18), 6295-6302.Synthesis of fluoro and azido derivatives of purine nucleosides from nucleoside 2',3'-cyclic sulfates. Bioorg. Khim. (1994), 20(11), 1226-30. Synthesis of modified oligomeric 2'-5' A analogs: potential antiviral agents. Helv. Chim. Acta (1991), 74(1), 7-23.Diethylaminosulfur trifluoride (DAST) as a fluorinating agent of pyrimidine nucleosides having a 2',3'-vicinal diol system. Chem. Pharm. Bull. (1990), 38(5), 1136-9. Synthesis of 9-(3-deoxy- and 2,3-dideoxy-3-fluoro-β-D-xylofuranosyl)guanines as potential antiviral agents. Tetrahedron Lett. (1989), 30(24), 3171-4. Synthesis and anti-HIV activity of various 2'- and 3'-substituted 2',3'-dideoxyadenosines: a structure-activity analysis. J. Med. Chem. (1987), 30(11), 2131-7. Adenosine 2',3'-ribo-epoxide. Synthesis, intramolecular degradation, and transformation into 3'-substituted xylofuranosyl nucleosides and the lyxo-epoxide. J. Org. Chem. (1974), 39(11), 1564-70. Fluoro sugar analogs of arabinosyl- and xylosylcytosines. J. Med. Chem. (1970), 13(2), 269-72. 9-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)adenine and 9-(3-deoxy-3-fluoro-β-D-arabinofuranosyl)adenine. Carbohyd. Res. (1968), 6(3), 347-54. 3',3'-Difluoro-3'-deoxythymidine: comparison of anti-HIV activity to 3'-fluoro-3'-deoxythymidine. J. Med. Chem. (1992), 35(18), 3369-72. Nucleic acid related compounds. 83. Synthesis of 3'deoxyadenosine-3'-spirocyclopropane, 3'-deoxyuridine-3'-spirocyclopropane, and 5'-deoxy-4',5'-methanoadenosine. Tetrahedron Lett. (1994), 35(21), 3445-8. Synthesis of 2',3'-didehydro-

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(1996), 52(23), 7929-7938. Nucleic acid related compounds. 83. Synthesis of 3'deoxyadenosine-3'-spirocyclopropane, 3'-deoxyuridine-3'-spirocyclopropane, and 5'-deoxy-4',5'-methanoadenosine. Some compounds of the present invention are commercially available at Sigma or Aldrich.

According to one embodiment, it will be appreciated that the amount of a compound of formula I of the present invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition for which treatment is required and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.01 to about 750 mg/kg of body weight per day, preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20 mg/kg/day.

The desired dose according to one embodiment is conveniently presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

In another embodiment, the compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

According to another embodiment of the present invention, the active ingredient is administered to achieve peak plasma concentrations of the active compound of from about 1 to about 75μM, preferably about 2 to 50 μM, most preferably about 3 to about 30 μM. This may be achieved,

for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 500 mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of formula I of the present invention may be administered as the raw chemical, it is preferable according to one embodiment of the invention, to present the active ingredient as a pharmaceutical formulation. The embodiment of the invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

According to one embodiment of the present invention, pharmaceutical formulations include but are not limited to those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods according to this embodiment include the step of bringing into association the active compound with liquid

carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

According to another embodiment, pharmaceutical formulation suitable for oral administration are conveniently presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules. In another embodiment, the formulation is presented as a solution, a suspension or as an emulsion. Still in another embodiment, the active ingredient is presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds of formula I according to an embodiment of the present invention are formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing an/or dispersing agents.

Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds of formula I, according to one embodiment of the present invention, are formulated as ointments, creams or lotions, or as a transdermal patch. Such transdermal patches may contain penetration enhancers such as linalool, carvacrol, thymol, citral, menthol and t-anethole. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid. In another embodiment, they are presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

According to one embodiment, the formulations suitable for vaginal administration are presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds, in one embodiment of the invention, are used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds, according to one embodiment of the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. In another embodiment, pressurized packs comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In another embodiment, the dosage unit in the pressurized aerosol is determined by providing a valve to deliver a metered amount.

Alternatively, in another embodiment, for administration by inhalation or insufflation, the compounds of formula I according to the present invention are in the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. In another embodiment, the powder composition is presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

In one embodiment, the above described formulations are adapted to give sustained release of the active ingredient.

The compounds of the invention may also be used in combination with other antiviral agents.

In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from protease inhibitors, polymerase inhibitors, and helicase inhibitors.

As used in this application, the term "interferon" include: interferon likes molecules such as interferon (IFN), interferon α-2a, interferon α-2b, consensus interferon (CIFN) and other types of interferons.

In one embodiment , the compounds of the invention may be employed together with at least one other antiviral agent chosen from interferon (IFN), interferon α-2a, interferon α-2b, consensus interferon (CIFN), ribavirin, amantadine, rimantadine, interleukine-12, ursodeoxycholic acid (UDCA), glycyrrhizin and silybum marianum.

In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from Interferon-α, Ribavirin and Amantadine.

In one embodiment, the compounds of the invention may be employed together with at least one other antiviral agent chosen from Interferon-α and Ribavirin (REBETRON).

In one embodiment, the compounds of the invention may be employed together Interferon-α.

In one embodiment, the compounds of the invention may be employed together with Ribavirin.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

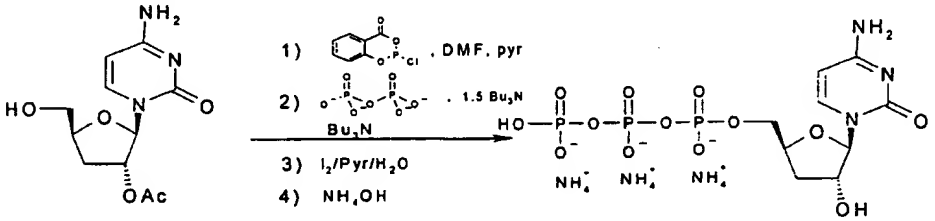
The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound (I) or a pharmaceutically acceptable salts thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone.

Appropriate doses will be readily appreciated by those skilled in the art.

The following examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.

Example 1. Preparation of 3'-DEOXYCYTIDINE 5'-TRIPHOSPHATE TRIAMMONIUM SALT (Compound #2)



Procedure: To a stirring suspension of 3'-deoxy-2'-acetoxycytidine (15.0 mg, 0.056 mmol) in dry DMF (0.60 ml) was added dry pyridine (0.20 ml) followed by a freshly prepared solution of 2-chloro-4 H-1,3,2-benzodioxaphosphorin-4-one 0.5 M in 1,4-dioxane (111 µl, 0.056 mmol). The mixture was stirred 30 minutes at room temperature, then tributylamine (36 µl, 0.152 mmol) and a solution of tributylammonium pyrophosphate 0.5 M in DMF (101 µl, 0.051 mmol) were added simultaneously. The mixture was stirred another 30 minutes. A solution of I2 1% in pyridine/H2O (98 :2) (1.01 ml, 0.081 mmol of I) was added and the mixture was stirred 30 minutes. The excess of iodine was destroyed by adding 0.2 ml of aqueous sodium bisulfite 5%. The mixture was stirred 15 minutes, then it was concentrated under reduced pressure to remove all solvents. The residue was dissolved in water, washed two times with methylene chloride and once with ethyl acetate. The aqueous layer was concentrated and purified by charcoal column as follow: about 400 mg of charcoal, placed over a thin layer of Celite in a funnel with fritted disk, was prewashed by passing methanol, then deionized water (by vaccuum). The crude residue was diluted in a minimum of water, acidified to pH 1-2 by adding few drops of HCl 1N, then placed on the top of the charcoal column. The column was eluted with deionized water (35 ml) in order to remove inorganic salts, then 0.5 N ammonia (15 ml) to collect the desired triphosphate. The collected triphophate was concentrated and diluted in deionized water (1 ml) and concentrated NH4OH (2 ml). The mixture was stirred one hour at room temperature to cleave the acetyl group, then concentrated to dryness. The residue was purified on a pad of C18 RP silica gel eluting with deionized water (the desired triphosphate comes out fast). The fractions containing the desired triphosphate were collected and lyophilized

to give the 3'-deoxycytidine 5'-triphosphate triammonium salt as a yellowish solid (18 mg, 69% yield, purity >85% evaluated by 1H and 31P-NMR).1H NMR (400 MHz, D2O) δ: 7.90 (d, 1 H, 7.5 Hz), 5.99 (d, 1 H, 7.5 Hz), 5.73 (s, 1 H), 4.55 (s, 1 H), 4.35 (d, 1 H, 5.0 Hz), 4.26 (m, 1 H), 4.04 (m, 1 H), 2.05 (m, 1 H), 1.94 (m, 1 H) ppm. 31P NMR (162 MHz, D2O) δ: -5.9 (br.s), -10.4 (d, 19 Hz), -21.5 (br.s) ppm.In a similar manner, the compounds of the invention can be obtained.

Example 2. Evaluation of Triphosphate Analogues

In The HCV RNA-Dependent RNA Polymerase AssayThe following references which are referenced in the example are all incorporated by reference:

1. Behrens, S., Tomei, L., De Francesco, R. (1996) *EMBO* 15, 12-22
2. Harlow, E, and Lane, D. (1988) *Antibodies: A Laboratory Manual*. Cold Spring Harbord Laboratory. Cold Spring Harbord. NY.
3. Lohmann, V., Körner, F., Herian, U., and Bartenschlager, R. (1997) *J. Virol.* 71, 8416-8428

Compounds were evaluated using an *in vitro* polymerase assay containing purified recombinant HCV RNA-dependent RNA polymerase (NS5B protein). HCV NS5B was expressed in insect cells using a recombinant baculovirus as vector. The experimental procedures used for the cloning, expression and purification of the HCV NS5B protein are described below. Following are details of the RNA-dependent RNA polymerase assays used to test the compounds.

Expression of the HCV NS5B protein in insect cells:

The cDNA encoding the entire NS5B protein of HCV-Bk strain, genotype 1b, was amplified by PCR using a plasmid

containing a cDNA version of the full-length HCV genome as template. The oligonucleotides used to amplify this HCV region were designed to introduce a *Nhe*I site followed by an ATG at the 5' end of the NS5B coding region as well as a *Bam*HI site at the 3'end immediately downstream of the translation stop codon. The amplified sequence, of 1.8 kb, was digested with *Nhe*I and *Bam*HI and ligated to a predigested pBlueBacII plasmid (Invitrogen). The resulting recombinant plasmid was designated pBac/NS5B. Sf9 cells were co-transfected with 3 µg of pBac/NS5B, together with 1 µg of linearized baculovirus DNA (Invitrogen), as described in the manufacturer's protocol. Following two rounds of plaque purification, an NS5B-recombinant baculovirus, BacNS5B, was isolated. The presence of the recombinant NS5B protein was determined by western blot analysis (Harlow and Lane, 1988) of BacNS5B-infected Sf9 cells, using a HCV NS5B specific rabbit polyclonal antiserum (anti-NS5B). Infections of Sf9 cells with this plaque purified virus were performed in one-liter spinner flasks at a cell density of 1.2 x 10^6 cells/ml and a multiplicity of infection of 5.

Preparation of a soluble recombinant NS5B protein:

Sf9 cells were infected as described above. Sixty hours post-infection, cells were harvested then washed twice with phosphate buffer saline (PBS). Total proteins were solubilized as described in Lohmann *et al.* **(1989)** with some modifications. In brief, proteins were extracted in three steps, S1, S2, S3, using lysis buffers (LB) I, LB II and LB III (Lohmann et al, 1997). The composition of LBII was modified to contain 0.1 % triton X-100 and 150 mM NaCl to reduce the amount of solubilized NS5B protein at this step. In addition, sonication of cell extracts was avoided throughout the protocol to preserve the integrity of the protein structure.

Purification of recombinant NS5B using fast protein liquid chromatography (FPLC):

Soluble NS5B protein in the S3 fraction was diluted to lower the NaCl concentration to 300 mM, then it incubated batchwise with DEAE sepharose beads (Amersham-Pharmacia) for 2 hrs at 4°C, as described by Behrens et al. **(1989)**. Unbound material was cleared by centrifugation for 15 min at 4°C, at 25 000 rpm using a SW41 rotor (Beckman). The supernatant was further diluted to lower the NaCl concentration to 200 mM and subsequently loaded, with a flow rate of 1 ml/min, on a 5 ml HiTrap® heparin column (Amersham-Pharmacia) connected to an FPLC® system (Amersham-Pharmacia). Bound proteins were eluted in 1 ml fractions, using a continuous NaCl gradient of 0.2 to 1 M, over a 25 ml volume. NS5B-containing fractions were identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), followed by western blotting using the anti-NS5B antiserum at a dilution of 1:2000. Positive fractions were pooled and the elution buffer was exchanged against a 50 mM $NaPO_4$ pH 7.0, 20 % glycerol, 0.5 % triton X-100 and 10 mM DTT, using a PD-10 column (Amersham-Pharmacia). The sample was then loaded onto a 1 ml HiTrap® SP column (Amersham-Pharmacia), with a flow rate of 0.1 ml/min. Bound proteins were eluted using a continuous 0 to 1 M NaCl gradient over a 15 ml volume. Eluted fractions were analyzed by SDS-PAGE and western blotting. Alternatively, proteins were visualized, following SDS-PAGE, by silver staining using the Silver Stain Plus kit (BioRad) as described by the manufacturer. Positive fractions were tested for RdRp activity (see below) and the most active ones were pooled, and stored as a 40 % glycerol solution at -70°C.

In vitro RNA-dependent RNA polymerase assays used to evaluate the triphosphate form of nucleoside analogues:

RdRp assays were conducted using *in vitro* transcribed heteropolymeric RNA templates.

RdRp reactions were performed in a total volume of 50 µl of a buffer consisting of 20 mM Tris-HCl pH 7.5, 1 mM DTT, 50 mM NaCl, 0.5 mM $MnCl_2$ and 5 mM $MgCl_2$. Standard HCV RdRp reactions contained 200 ng of purified NS5B protein. The substrate mixture included in the assay depended on the base of the nucleoside triphosphate to be tested (adenine, guanine, cytosine or uracil analogue). The NTP substrate with a similar base to that of the inhibitor, was added at twice the measured Km. This concentration included 5 µCi (3000 Ci/mmol) of a [^{32}P] version of this nucleotide. The remaining three substrates were used at 100 µM. The measured Kms for the four substrates were as follows: 18 µM for ATP, 0.5 µM for CTP and GTP, and 1.2 µM for UTP. Following a two hour incubation at 22°C, reactions were stopped by the addition of 100 µg of sonicated salmon sperm DNA (Life Technologies) and 1 ml of 10 % trichloroacetic acid (TCA)-0.5 % tetrasodium pyrophosphate (PPi). Nucleic acids were precipitated at 4°C for 30 min after which samples were filtered on GF/C glass microfiber filters (Millipore). Membranes were subsequently washed with 25 ml of a 1% TCA-0.1 % PPi solution, then air dried. Incorporated radioactivity was quantified using a liquid scintillation counter (1450-Microbeta, Wallac).

Heteropolymeric RNA templates were generated by run-off transcription. As template for these transcription reactions, a recombinant pcDNA3 plasmid (Invitrogen) containing a cDNA version of the HCV genome was used and referred to as pcDNA/HCVf1. In vitro transcriptions were performed using the MEGAscriptTM kit (Ambion), as suggested by the manufacturer. In brief, the plasmid pcDNA/HCVf1 was linearized with EcoRI to generate a truncated HCV transcript of about 6900 nucleotides. Linearized DNA was extracted with a one to one volume of

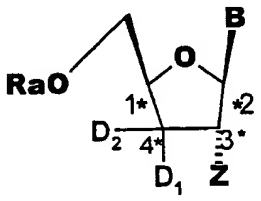
phenol/chloroform, precipitated with ethanol, then 1 µg of this linearized DNA was used as template in T7 RNA polymerase-driven in vitro transcription reactions. Transcripts were extracted using the TRIZOL® reagent (Life Technologies) and an aliquot (1 µg) was used as template in RdRp assays.

Compound	HCV polymerase
	IC_{50}
COMPOUND#2	0.036µM
COMPOUND#4	0.3µM
COMPOUND#6	0.26µM
COMPOUND#8	1.98µM
COMPOUND#10	6.4µM
COMPOUND#12	0.048µM
COMPOUND#14	3.1µM
COMPOUND#16	0.36µM
COMPOUND#18	6.88µM
COMPOUND#20	0.18µM
COMPOUND#22	0.12µM
COMPOUND#24	0.055µM
COMPOUND#26	0.91µM
COMPOUND#28	2.1µM
COMPOUND#30	2.9µM
COMPOUND#32	6.8µM
COMPOUND#54	9.0µM

CLAIMS

We claim:

1. A method for the treatment or prevention of an hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound having the formula Ib or a pharmaceutically acceptable salt thereof:

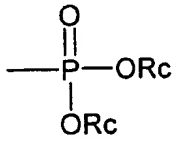


(Ib)

wherein

B is chosen from a purine, a pyrimidine or an analogue thereof;

Ra is chosen from H, monophosphate, diphosphate, triphosphate, carbonyl substituted with a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, and



wherein each **Rc** are independently chosen from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl and an hydroxy protecting group; and

Z is **ORb**, wherein **Rb** is chosen from of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} acyl, or an hydroxy protecting group

D_1 and D_2 are independently selected from N_3, F, or H , D_1 and D_2 can also be joined to be chosen from C_3-cycloalkyl, $-=CH_2$, or $-=CF_2$,;

with the proviso that when **B** is adenine, **Z** is **ORb**, D_1 is H, D_2 is H and **Rb** is H, **Ra** is not triphosphate or H.

2. A method according to claim 1 wherein **Z** is OH.

3. A method according to claim 2 wherein D_1 is H and D_2 is F.

4. A method according to claim 2 wherein **Ra** is chosen from H, monophosphate, diphosphate, triphosphate.

5. A method according to claim 2 wherein **Ra** is triphosphate.

6. A method according to claim 2 wherein **Ra** is H.

7. A method according to claim 3 wherein **Ra** is chosen from H, monophosphate, diphosphate, triphosphate.

8. A method according to claim 3 wherein **Ra** is triphosphate.

9. A method according to claim 3 wherein **Ra** is H.

10. A method according to claim 2 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-

amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl; each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

11. A method according to claim 3 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, uracil-1-yl, 3-carboxamido-1,2,4-triazol-1-yl, 3-deaza-adenin-9-yl, 3-deaza-guanin-9-yl, 3-deaza-inosin-9-yl, 3-deaza-2-amino-purin-9-yl, 3-deaza-2-amino-6-chloro-purin-9-yl 3-deaza-2-6-diamino-purin-9-yl, 7-deaza-adenin-9-yl, 7-deaza-guanin-9-yl, 7-deaza-inosin-9-yl, 7-deaza-2-amino-purin-9-yl, 7-deaza-2-amino-6-chloro-purin-9-yl, 7-deaza-2-6-diamino-purin-9-yl, 7-deaza-8-aza-adenin-9-yl, 7-deaza-8-aza-guanin-9-yl, 7-deaza-8-aza-inosin-9-yl, 7-deaza-8-aza-2-amino-purin-9-yl, 7-deaza-8-aza-2-amino-6-chloro-purin-9-yl, 7-deaza-8-aza-2-6-diamino-purin-9-yl, 8-aza-adenin-9-yl, 8-aza-guanin-9-yl, 8-aza-inosin-9-yl, 8-aza-2-amino-purin-9-yl, 8-aza-2-amino-6-chloro-purin-9-yl, 8-aza-2-6-diamino-purin-9-yl, 5-aza-thymin-1-yl, 5-aza-cytosin-1-yl, 5-aza-uracil-1-yl, 6-aza-thymin-1-yl, 6-aza-cytosin-1-yl, 6-aza-uracil-1-yl; each of which is unsubstituted or substituted by at least one of NHR_3, C_{1-6}alkyl, $-OC_{1-6}$alkyl, Br, Cl, F, I or OH, wherein R_3 is H, C_{1-6}alkyl or C_{1-6}acyl.

12. A method according to claim 2 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).

13. A method according to claim 3 wherein **B** is chosen from adenin-9-yl, guanin-9-yl, inosin-9-yl, 2-amino-purin-9-yl, 2-amino-6-chloro-purin-9-yl, 2-6-diamino-purin-9-yl, thymin-1-yl, cytosin-1-yl, 5-fluoro-cytosin-1-yl, uracil-1-yl, 5-fluorouracil or 1,2,4-triazole-3-carboxamide base (ribarivin base).

14. A method according to claim 1 wherein the compound of formula I is chosen from:

Compound #1:3'-deoxycytidine;
Compound #2: 3'-deoxycytidine-5'triphosphate;
Compound #3:5-Fluoro-3'-deoxycytidine;
Compound #4:5-Fluoro-3'-deoxycytidine-5'triphosphate;
Compound #5:3'-deoxyuridine;
Compound #6:3'-deoxyuridine-5'triphosphate;
Compound #7:5-Fluoro-3'-deoxyuridine;
Compound #8:5-Fluoro-3'-deoxyuridine-5'triphosphate;
Compound #9:3'-deoxythymidine;
Compound #10:3'-deoxythymidine-5'triphosphate;
Compound #11:3'-deoxyguanosine;
Compound #12:3'-deoxyguanosine-5'triphosphate;
Compound #13:2-N-acetyl-3'-deoxyguanosine;
Compound #14:2-N-acetyl-3'-deoxyguanosine-5'triphosphate;
Compound #15:5-Methyl-3'-deoxycytidine;
Compound #16:5-Methyl-3'-deoxycytidine-5'triphosphate;
Compound #17:5-Iodo-3'-deoxycytidine;
Compound #18:5-Iodo-3'-deoxycytidine-5'triphosphate;

Compound #19:5-Chloro-3'-deoxycytidine;

Compound #20:5-Chloro-3'-deoxycytidine-5'triphosphate;

Compound #21:3'-fluoro-3'-deoxyguanosine;

Compound #22:3'-fluoro-3'-deoxyguanosine -5'triphosphate;

Compound #23:3'-fluoro 3'-deoxycytidine;

Compound #24:3'-fluoro 3'-deoxycytidine-5'triphosphate;

Compound #25:5-Iodo-3'-deoxycytidine;

Compound #26:5-Iodo-3'-deoxycytidine-5'triphosphate;

Compound #27:5-Chloro -3'-deoxyuridine;

Compound #28:5-Chloro -3'-deoxyuridine-5'triphosphate;

Compound #29:5-Bromo -3'-deoxyuridine;

Compound #30:5-Bromo -3'-deoxyuridine-5'triphosphate;

Compound #31:6-Chloro-3'-deoxyguanosine;

Compound #32:6-Chloro -3'-deoxyguanosine -5'triphosphate;

Compound #33:3'-spirocyclopropyl-3'-deoxyguanosine;

Compound #34:3'-spirocyclopropyl-3'-deoxyguanosine - 5'triphosphate;

Compound #35:3'-difluoro-spirocyclopropyl-3'-deoxyguanosine;

Compound #36:3'-difluoro-spirocyclopropyl-3'-deoxyguanosine -5'triphosphate;

Compound #37:3'-methylene-3'-deoxyguanosine;

Compound #38:3'-methylene-3'-deoxyguanosine - 5'triphosphate;

Compound #39:3'-difluromethylene 3'-deoxyguanosine;

Compound #40:3'-difluromethylene 3'-deoxyguanosine - 5'triphosphate;

Compound #41:3'-spirocyclopropyl-3'-deoxycytidine;

Compound #42:3'-spirocyclopropyl-3'- deoxycytidine - 5'triphosphate;

Compound #43:3'-difluoro-spirocyclopropyl-3'-deoxycytidine;

Compound #44:3'- difluoro-spirocyclopropyl-3'-deoxycytidine -5'triphosphate;

Compound #45:3'-methylene-3'- deoxycytidine;

Compound #46:3'-methylene-3'- deoxycytidine - 5'triphosphate;

Compound #47:3'-difluromethylene 3'- deoxycytidine;

Compound #48:3'-difluromethylene 3'- deoxycytidine - 5'triphosphate;

Compound #49:9-β-D-xylofuranosyl-guanosine;

Compound #50:9-β-D-xylofuranosyl-guanosine - 5'triphosphate;

Compound #51:9-β-D-xylofuranosyl-cytidine;

Compound #52:9-β-D-xylofuranosyl-cytidine - 5'triphosphate;

Compound #53: 3'-azido-3'- deoxycytidine;

Compound #54:3'-azido-3'- deoxycytidine 5'triphosphate;or a pharmaceutically acceptable salt thereof.

15. The method according to anyone of claims 1 to 14 wherein said compound is used in combination with at least one further therapeutic agent chosen from interferon (IFN), interferon α-2a, interferon α-2b, consensus interferon (CIFN), ribavirin, amantadine, rimantadine, interleukine-12, ursodeoxycholic acid (UDCA), glycyrrhizin and silybum marianum.

16. Use of a compound of formula (Ib) as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a hepatitis C infection.

17. An anti-flavivirus pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (1b), as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

18. Use of a compound of formula (Ib) as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a Flavivirus infection.

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Request Created Date/Time:	Friday, June 20, 2003 12:56:00 Central
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1997 Copr.L.Dec. P 27,631, 42 U.S.P.Q.2d 1467, 10 Fla. L. Weekly Fed. C 835
(Cite as: 110 F.3d 749)

▷

United States Court of Appeals,
Eleventh Circuit.

JACOB MAXWELL, INCORPORATED,
Plaintiff-Counter-Defendant-Appellant, Cross-Appellee,
v.
Michael VEECK, Individually and as General Partner of the Fort Myers Miracle Baseball Club Partnership, et al., Defendants,
John Kuhn, Movant,
Marvin Goldclang, Individually and as General Partner of the Fort Myers Miracle Baseball Club Partnership, Greater Miami Baseball Club Limited Partnership,
Defendants-Appellees, Cross-Appellants,
Baseball Company of America, a Florida Limited Partnership, Baseball Corp. of America, Inc., a New Jersey Corporation,
Defendants-Counter-Claimants-Appellees, Cross-Appellants.

No. 96-2636.

April 18, 1997.
Rehearing Denied May 13, 1997.

Holder of copyright for song written to promote minor league baseball team brought copyright infringement action against team. The United States District Court for the Middle District of Florida, No. 93-372-CIV-FTM-24D, Susan C. Bucklew, J., entered judgment in favor of team, and copyright holder appealed. The Court of Appeals, Levin H. Campbell, Senior Circuit Judge, sitting by designation, held that: (1) copyright holder granted minor league baseball team implied, nonexclusive license to play copyrighted song at team's games, and (2) even assuming that team's conduct breached parties' oral understanding, team's playing of song at its games with holder's permission did not violate holder's copyright.

Affirmed.

West Headnotes

[1] Copyrights and Intellectual Property 48
99k48 Most Cited Cases

Copyright holder granted minor league baseball team implied, nonexclusive license to play copyrighted song at team's games, although parties contemplated exclusive license in their initial negotiations; songwriter created song at team's request and handed master tape over, intending that team play song at its games, and did not object when song was played, even though copyright holder had not been paid. 17 U.S.C.A. §§ 101, 204(a).

[2] Copyrights and Intellectual Property 48
99k48 Most Cited Cases

In contrast to exclusive license, nonexclusive license to use copyright may be granted orally, or may even be implied from conduct. 17 U.S.C.A. §§ 101, 204(a).

[3] Federal Courts 429
170Bk429 Most Cited Cases

Generally, state law governs interpretation of copyright contracts, unless particular state rule of construction would so alter rights granted by copyright statutes as to invade scope of copyright law or violate its policies.

[4] Copyrights and Intellectual Property 48
99k48 Most Cited Cases

District court was required to look at alternatives beyond parties' intended exclusive copyright-licensing arrangement; where federal copyright law rendered parties' oral agreement unenforceable insofar as it provided for transfer of exclusive copyright. 17 U.S.C.A. § 204(a).

[5] Copyrights and Intellectual Property 53(1)
99k53(1) Most Cited Cases

Even assuming that minor league baseball team's conduct in failing to reimburse copyright holder's costs in creating song for team and to publicly acknowledge songwriter at games as song's creator breached parties' oral understanding, team's playing of song at its games pursuant to holder's permission did not violate holder's copyright; such breach only entitled holder to rescind agreement and revoke its permission to play song in future.

[6] Copyrights and Intellectual Property ⇨48
99k48 Most Cited Cases

Minor league baseball team's payment of copyright holder's costs and public recognition of authorship when it played copyrighted song at its games were not conditions precedent to team's right to play songs, where holder, through its president, expressly granted team permission to play song before payment was tendered or recognition received, and did not thereafter withdraw permission, although he attended many games and heard song played, without payment or recognition. Restatement (Second) of Contracts § 225.

***750** Joel S. Perwin, Podhurst, Orseck, Josefsberg, Eaton, Meadow, Olin & Perwin, P.A., Miami, FL, for Appellants.

Thomas G. Whaley, Minneapolis, MN, for Appellees.

Appeal from the United States District Court for the Middle District of Florida.

Before CARNES, Circuit Judge, and CLARK and CAMPBELL [FN*], Senior Circuit Judges.

FN* Honorable Levin H. Campbell, Senior U.S. Circuit Judge for the First Circuit, sitting by designation.

***751** LEVIN H. CAMPBELL, Senior Circuit Judge:

This appeal concerns an unhappy dispute between the composer of a song entitled "Cheer! The Miracle Is Here" and a minor league baseball team, known as the Miracle, for whose promotion the song was written. After the parties' relations turned sour, the composer sued the Miracle claiming that its playing of the song at games had been a breach of copyright. Rejecting that contention, the district court awarded summary judgment to the Miracle and ruled that the Miracle had received an oral nonexclusive license authorizing the use that it made of the copyrighted song, and that the composer's remedy, if any, lay in a state court contract action for payment and damages. The composer has appealed, and the Miracle has cross-appealed from the district court's denial of its request for attorney's fees.

I.

We state the facts in the light most favorable to the non-moving party, Plaintiff-Appellant Jacob-Maxwell, Inc. ("JMI").

In the spring of 1993, James Albion, president of JMI, agreed to write a team song for the Miracle, a minor league baseball team. Albion agreed to write the song free of charge, to provide the Miracle with the Digital Audio Tape master, and to grant the Miracle an exclusive license. In return, Albion asked only that the Miracle pay his out-of-pocket production costs and that the team credit him as the author any time the song was played at games or distributed on cassette tapes. Albion told Michael Veeck, the Miracle's Executive Director, that his production costs would be somewhere between $800 and $1100.

Albion wrote and produced the song, incurring production expenses of $1050, and assigned ownership rights to JMI. He delivered a master tape (though not the Digital Audio Tape master) to John Kuhn, the Miracle's Director of Marketing and Promotion, on July 2, 1993, and requested payment. Kuhn told him he could not issue a check immediately but asked if he could play the song at the next day's game regardless. Albion agreed.

Over the course of the summer, the Miracle played the song many times at games, never giving Albion the promised authorship credit. Albion was present at many of these games. Albion repeatedly demanded payment, and once communicated his expectation that the lyrics and credits would be handed out to the fans, but did not withdraw his permission to play the song at games. To the contrary, in July 1993, Albion wrote to Kuhn urging the Miracle to continue to perform the song publicly.

On August 9, Albion provided the Miracle with a written invoice. On August 30, the Miracle tendered Albion a check for $500, telling him the rest would be handled later. Because the check was not marked "partial payment," Albion refused to accept it. On September 21, 1993, JMI formally registered the song with the United States Copyright

Office, and on October 12th JMI's attorney wrote to the Miracle, notifying the team that its use of the song constituted copyright infringement. The team last played the song on August 27, 1993.

JMI sued the owners and operators of the Miracle Baseball Club of Ft. Myers, Florida, alleging copyright infringement and breach of contract. The district court granted the defendants' motion for summary judgment on the copyright claim, holding that Albion had, by his conduct, granted the Miracle a nonexclusive license to play the song at the times it did. The court dismissed the pendent state law breach of contract claim without prejudice. [FN1]

> FN1. The defendants' state law counterclaim was likewise dismissed without prejudice.

II.

[1] On appeal, JMI argues that because the oral agreement had been for an exclusive license, the district court erred in finding an implied nonexclusive license.

The Copyright Act provides, "A transfer of copyright ownership, other than by operation of law, is not valid unless an instrument of conveyance, or a note or memorandum of the transfer, is in writing and signed by the ***752** owner of the rights conveyed or such owner's duly authorized agent." 17 U.S.C. § 204(a). It is undisputed that any arrangement between the parties for granting an exclusive license to the Miracle was never written down and that, therefore, no valid transfer to the team of copyright ownership under the Copyright Act took place.

[2] In contrast to an exclusive license, a nonexclusive license to use a copyright " 'may be granted orally, or may even be implied from conduct.' " *Effects Associates, Inc. v. Cohen,* 908 F.2d 555, 558 (9th Cir.1990) (quoting 3 M. Nimmer & D. Nimmer, *Nimmer on Copyright* § 10.03[A], at 10-36 (1989)), *cert. denied sub nom. Danforth v. Cohen,* 498 U.S. 1103, 111 S.Ct. 1003, 112 L.Ed.2d 1086 (1991). This is true because 17 U.S.C. § 101 excludes the assignment of nonexclusive licenses from the definition of "transfer of copyright ownership."

The district court, relying on the Ninth Circuit's decision in *Effects Associates,* determined that Albion had impliedly granted the Miracle a nonexclusive license by initially giving permission to play the song at games and by failing to object despite his knowledge that the team was continuing to play the song publicly. In *Effects Associates,* the Ninth Circuit held that a special effects company had granted a movie producer an implied nonexclusive license to use the special effects footage it had created. The court reasoned that because the special effects company had "created a work at defendant's request and handed it over, intending that defendant copy and distribute it," it had impliedly granted the defendant a nonexclusive license. *Id.*

Similarly, in this case Albion created the song at the Miracle's request and handed a master tape over, intending that the Miracle play the song at its games. But, JMI sees an important distinction between this case and *Effects Associates.* There, "no one said anything about who would own the copyright in the footage," *id.* at 556, but here the plaintiff orally indicated an intention to grant to the defendant an exclusive license.

[3] JMI argues that under Florida contract law, [FN2] it was error for the court to infer the creation of a *nonexclusive* license from the parties' conduct when they had explicitly agreed, albeit in an unenforceable oral exchange, to an *exclusive* license. *See Excelsior Insurance Company v. Pomona Park Bar & Package Store,* 369 So.2d 938, 942 (Fla.1979) (holding that courts may not "rewrite contracts, add meaning that is not present, or otherwise reach results contrary to the intentions of the parties"); *Rigel v. National Casualty Company,* 76 So.2d 285, 286 (Fla.1954) (holding that courts should not add a meaning to clear contract language); *Indian Harbor Citrus, Inc. v. Poppell,* 658 So.2d 605, 606 (Fla. 4th Dist.Ct.App.) (holding that custom or usage cannot be used to contradict an express contract), *review denied,* 666 So.2d 144 (Fla.1995); *Flagship National Bank v. Gray Distribution Systems, Inc.,* 485 So.2d 1336, 1340 (Fla. 3d Dist.Ct.App.1986) (holding that when the express terms of a contract conflict with the practice of the parties, the express terms of the contract control), *review denied,* 497 So.2d 1217

(Fla.1986).

FN2. As a general rule, state law governs the interpretation of copyright contracts, unless a particular state rule of construction would "so alter rights granted by the copyright statutes as to invade the scope of copyright law or violate its policies." *Fantastic Fakes, Inc. v. Pickwick International, Inc.*, 661 F.2d 479, 483 (5th Cir.1981). *See also* 3 M. Nimmer & D. Nimmer, *Nimmer on Copyright* § 12.01[A], at 12-8 n. 19 (1996).

[4] We do not find these cases controlling here. They either involve situations where parties seek to modify fully enforceable contracts by reference to the rule of interpretation which holds that an ambiguity in a contract is to be construed against the drafter or deal with attempts by a party to modify a clear contract term by reference to the parties' course of dealings or other extrinsic matters. This case does not present an analogous situation. Here federal copyright law renders the parties' oral agreement unenforceable insofar as it provided for the transfer of an exclusive copyright. In these circumstances, a court has no choice but to look at alternatives beyond the parties' intended arrangement.

*753 Like the district court, we conclude that while it may well be that the parties in their initial negotiations contemplated an exclusive license, JMI cannot reasonably deny, given its subsequent conduct here, that it granted to the Miracle the sort of lesser, nonexclusive license to play the piece during the summer of 1993 that federal law recognizes may result from a purely oral transaction.

Albion's approving conduct--his granting of permission to the Miracle on July 2, 1993 to play his song at the next day's game even though he had not yet been paid, his attendance without demur at subsequent games at which the song was played, his letter to Kuhn urging the Miracle to continue to play the song at games, and his failure to withdraw permission until October--clearly expressed Albion's permission for the Miracle to play the song when it did. Implicit in that permission was a promise not to sue for copyright infringement--a promise that at least one court has found to be the essence of a nonexclusive license. *See In re CFLC, Inc.*, 89 F.3d 673, 677 (9th Cir.1996) ("[A] nonexclusive patent license is, in essence, 'a mere waiver of the right to sue' the licensee for infringement.") (quoting *De Forest Radio Telephone & Telegraph Co. v. United States*, 273 U.S. 236, 242, 47 S.Ct. 366, 368, 71 L.Ed. 625 (1927)). We think it follows that until permission was withdrawn in October, JMI granted to the Miracle a nonexclusive license to play the song at games.

In so saying, we do not suggest that Albion and JMI waived their rights to be compensated by the Miracle in accordance with their oral understanding. What they waived was any right to sue for breach of copyright on account of the playing of the song while the license was in effect. As discussed in the following section, the Miracle's failure to provide the agreed quid pro quo could not, on the facts of this case, invalidate the legal effect of Albion's permission to play.

III.

[5] JMI argues that even assuming it gave the Miracle an oral, nonexclusive license to play the song, that right should be treated as having been cancelled in its entirety by the Miracle's material breach of their oral understanding when it failed both to reimburse JMI's costs and publicly to acknowledge Albion at games as the song's creator. But even assuming arguendo that the Miracle's conduct constituted a material breach of the parties' oral understanding, this fact alone would not render the Miracle's playing of the song pursuant to JMI's permission a violation of JMI's copyright. Such a breach would do no more than *entitle* JMI to rescind the agreement and revoke its permission to play the song in the future, actions it did not take during the relevant period. One party's breach does not automatically cause recision of a bilateral contract. *See Fosson v. Palace (Waterland), Ltd.*, 78 F.3d 1448, 1455 (9th Cir.1996) (recognizing "the rule applied in other circuits that once a non-breaching party to an express copyright license obtains *and exercises* a right of rescission by virtue of a material breach of the agreement, any further distribution of the copyrighted material would constitute infringement") (emphasis added); *Hyman v. Cohen*, 73 So.2d 393, 397 (Fla.1954) ("

110 F.3d 749
1997 Copr.L.Dec. P 27,631, 42 U.S.P.Q.2d 1467, 10 Fla. L. Weekly Fed. C 835
(Cite as: 110 F.3d 749)

'A material breach, as where the breach goes to the whole consideration of the contract, gives to the injured party the *right* to rescind the contract or to treat it as a breach of the entire contract....' ") (quoting 12 Am.Jur. *Contracts* § 389) (emphasis added); 3 M. Nimmer & D. Nimmer, *Nimmer on Copyright* § 10.15[A], at 10-125-126 (1996) (" *Upon such rescission,* the assignment or license is terminated and the copyright proprietor may hold his former grantee liable as an infringer for *subsequent* use of the work.") (emphasis added).

Since Albion on July 2, 1993 expressly gave his permission to the Miracle to play his song at the next game, renewed this permission by letter that same month, and did not thereafter withdraw permission until some time after the Miracle had last played the song publicly, the Miracle never played the song without permission and is not liable for copyright infringement.

[6] This is not a case where payment of JMI's costs and public recognition of authorship were made conditions precedent to the granted right to play. *See Restatement (Second) of Contracts* § 225 (1981) . In such a case, absent performance of the conditions, ***754** the "license" would not have issued and the Miracle's public performances of the song would have violated JMI's copyright. *See Fantastic Fakes,* 661 F.2d at 483; 3 M. Nimmer & D. Nimmer, *Nimmer on Copyright* § 10.15[A], at 10-121 (1996).

But Albion did not make payment and recognition conditions precedent to the permission he gave to play the song. "A condition is an event, not certain to occur, which must occur, unless its non-occurrence is excused, before performance under a contract becomes due." *Restatement (Second) of Contracts* § 224 (1981). "Conditions precedent are disfavored and will not be read into a contract unless required by plain, unambiguous language." *Effects Associates,* 908 F.2d at 559 n. 7. On July 2, 1993, JMI, through its president, Albion, expressly granted the Miracle permission to play the song before payment was tendered or recognition received. Thereafter, Albion did not withdraw permission although he attended many games and heard the song played, still without payment or recognition, on various occasions. Indeed, he wrote to Kuhn encouraging the Miracle to continue to play the song. Under these circumstances, we cannot say that JMI's permission to play was conditioned on prior payment and public recognition.

IV.

While for the above reasons, JMI cannot recover breach of copyright damages from the Miracle for the latter's playing of the song, this does not end the matter.

JMI asserts that the Miracle made and broke its promise to pay JMI's expenses and to give public recognition and credit to the song's composer. While payment and recognition were not conditions precedent to playing the song, the district court recognized that JMI may be entitled to recover in a state action its damages from the Miracle's failure to perform these promises. Nothing herein is intended to suggest that the Miracle's treatment of JMI and Albion was either legally correct or such as to shield them from liability for their conduct. The only issue before the district court was JMI's right to recover under federal law for copyright infringement.

V.

In its cross-appeal, the Miracle contends that the district court abused its discretion in declining to award it attorney's fees under 17 U.S.C. § 505. That section states, in relevant part, "Except as otherwise provided by this title, the court may also award a reasonable attorney's fee to the prevailing party as part of the costs." Under this statute, attorney's fees are at the court's discretion. *Fogerty v. Fantasy, Inc.,* 510 U.S. 517, 534, 114 S.Ct. 1023, 1033, 127 L.Ed.2d 455 (1994).

The Supreme Court has provided a nonexclusive list of factors which district courts may take into account when determining whether or not to award a prevailing party attorney's fees under § 505. "These factors include 'frivolousness, motivation, objective unreasonableness (both in the factual and in the legal components of the case) and the need in particular circumstances to advance considerations of compensation and deterrence.' " *Id.* (quoting *Lieb v. Topstone Industries, Inc.,* 788 F.2d 151, 156 (3d Cir.1986)). After considering these factors, we are unable to say that the district court abused its discretion in refusing to award attorney's fees.

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Affirmed.

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